Critical Care

REVIEW

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Advanced Life Support Update

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Abstract

This article is one of ten reviews selected from the Annual Update in Intensive Care and Emergency Medicine 2022. Other selected articles can be found online at https://www.biomedcentral.com/collections/annualupdate2022. Further information about the Annual Update in Intensive Care and Emergency Medicine is available from https://link.springer.com/bookseries/8901.

Introduction

Cardiac arrest remains a significant cause of morbidity and mortality around the world. The International Liaison Committee on Resuscitation (ILCOR) is a collaboration of resuscitation councils from around the world that work together with the shared vision of saving more lives globally through resuscitation [1]. ILCOR has been synthesizing evidence relating to resuscitation to produce consensus on science and treatment recommendations for many years. Recent evidence evaluations have been informed by systematic reviews of the literature and the Grading of Recommendations Assessment, Development and Evaluation (GRADE) method to assess the certainty in evidence and the strength of recommendations [2]. These evidence evaluations are translated into practice by regional resuscitation councils from around the world. In Europe, the European Resuscitation Council (ERC) produces high quality, multi-disciplinary, evidenced-based guidelines for resuscitation [3]. In this chapter, we summarize key practice recommendations drawn from the most recent guideline updates relating to advanced life support (ALS) [4, 5], post-resuscitation care, and prognostication [6].

Setting the Scene: Epidemiology and Outcomes

Data from the ERC Registries for Cardiac Arrest (EuReCa) studies report that the incidence of resuscitation attempts for out-of-hospital cardiac arrest (OHCA) ranges from 19 to 104 per 100,000 population per year [7, 8]. An international review of registries reported an incidence within these ranges in the USA, Canada, Australia, Asia, and Japan [9]. Most OHCAs in Europe have medical/cardiac causes and present with an initially nonshockable rhythm (80%) [7]. Return of spontaneous circulation (ROSC) is achieved in one third of patients with OHCA (range 8–42%) and the overall rate of survival to discharge is in the region of 8% (range 0–18%) [7]. Those with a witnessed cardiac arrest, with early bystander cardiopulmonary resuscitation (CPR), and with public access defibrillation have the best chances of survival [10]. Fewer data are available on the epidemiology of in-hospital cardiac arrest (IHCA) [11, 12]. The incidence of IHCA in the UK and USA is between 1.6 and 10 cases per 1000 admissions. Like OHCA, the majority of IHCAs are associated with nonshockable rhythms from a combination of respiratory and cardiac causes. A higher proportion of arrests are witnessed, and CPR is started almost simultaneously with the arrival of the ALS team within minutes. The rate of survival to hospital discharge is approximately 25%, 2–3 times higher than for OHCA [11].
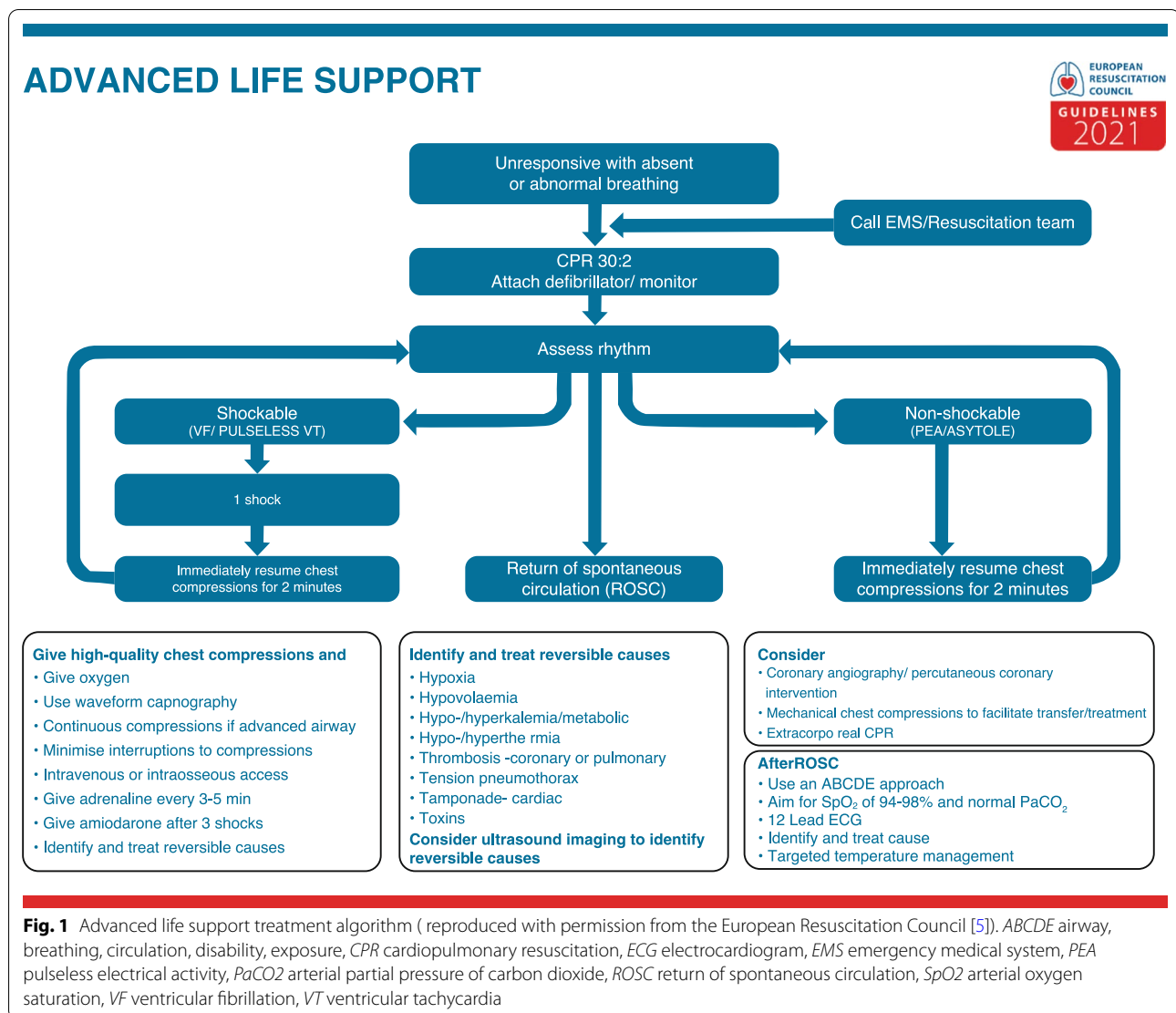
Differences in case numbers likely reflect differences in system responses to cardiac arrest, the threshold as to when resuscitation is commenced and continued, as well as differences in risk from the resident population

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ADVANCED LIFE SUPPORT

EUROPEAN
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GUIDELINES
2021

Unresponsive with absent
or abnormal breathing

Call EMS/Resuscitation team

CPR 30:2
Attach defibrillator/ monitor

Assess rhythm

Shockable
(VF/ PULSELESS VT)

1 shock

Immediately resume chest
compressions for 2 minutes

Return of spontaneous
circulation (ROSC)

Non-shockable
(PEA/ASYTOLE)

Immediately resume chest
compressions for 2 minutes

Give high-quality chest compressions and
• Give oxygen
• Use waveform capnography
• Continuous compressions if advanced airway
• Minimise interruptions to compressions
• Intravenous or intraosseous access
• Give adrenaline every 3-5 min
• Give amiodarone after 3 shocks
• Identify and treat reversible causes

Identify and treat reversible causes
• Hypoxia
• Hypovolaemia
• Hypo-/hyperkalemia/metabolic
• Hypo-/hyperthermia
• Thrombosis -coronary or pulmonary
• Tension pneumothorax
• Tamponade- cardiac
• Toxins
**Consider ultrasound imaging to identify
reversible causes**

Consider
• Coronary angiography/ percutaneous coronary
  intervention
• Mechanical chest compressions to facilitate transfer/treatment
• Extracorpo real CPR

AfterROSC
• Use an ABCDE approach
• Aim for SpO_2 of 94-98% and normal $PaCO_2$
• 12 Lead ECG
• Identify and treat cause
• Targeted temperature management

Fig. 1 Advanced life support treatment algorithm (reproduced with permission from the European Resuscitation Council [5]). *ABCDE* airway, breathing, circulation, disability, exposure, *CPR* cardiopulmonary resuscitation, *ECG* electrocardiogram, *EMS* emergency medical system, *PEA* pulseless electrical activity, *PaCO2* arterial partial pressure of carbon dioxide, *ROSC* return of spontaneous circulation, *SpO2* arterial oxygen saturation, *VF* ventricular fibrillation, *VT* ventricular tachycardia

characteristics [11, 12]. Differences in outcomes can often be explained by the proportion of cardiac arrests where resuscitation is attempted and, where relevant, the community response to cardiac arrest (particularly bystander CPR and defibrillation). The time taken for the ALS team to arrive, how health systems approach discontinuation of resuscitation, access to and the quality of post-resuscitation care as well as neuroprognostication and withdrawal of life sustaining treatment practices likely also contribute to variation in outcomes [12]. The importance of functional recovery beyond the blunt categorization of outcomes into favorable or unfavorable neurological outcomes has been emphasized in recent reviews [12, 13]. Many patients classified as surviving with a favorable neurological outcome have significant functional impairments. Common problems reported

in survivors of cardiac arrest include fatigue, cognitive problems (slowing or problems with attention or memory), emotional problems (anxiety, depression, post-traumatic stress), and physical impairments. These problems adversely affect health related quality of life and can reduce ability to return to work and social par ticipation. Guidelines highlight the paucity of detailed follow-up for cardiac arrest survivors and lack of a strong evidence base to inform rehabilitation strategies [12].

Advanced Life Support Treatment Algorithm

The ALS treatment algorithm (Fig. 1) provides a framework for the assessment and treatment of cardiac arrest. Agonal breathing (also known as terminal gasping) is relatively common in the early stages after cardiac arrest [14]. Therefore, a diagnosis of cardiac arrest should be

considered in any patient who is unresponsive with absent or abnormal breathing [14]. The use of advanced monitoring (e.g., electrocardiograph [EKG], arterial blood pressure, and capnography) may aid rapid diagnosis [5, 10]. Palpation of a central pulse to confirm cardiac arrest should be undertaken with caution and with an awareness of a high false positive rate (i.e., a pulse is thought to be present but is actually absent) [15]. Resuscitation should be started with chest compressions first, unless the person is attached to a defibrillator at the time of a witnessed cardiac arrest, in which case up to three successive shocks may be delivered. Cough CPR, fist pacing, and precordial thump are generally ineffective and their use should not delay definitive treatment with CPR and defibrillation [16].

The algorithm splits treatments according to whether the initial rhythm is shockable or non-shockable. Whilst the person remains in a shockable rhythm, the priority is high quality CPR and attempted defibrillation. It is important to minimize interruptions in CPR, particularly before and after delivering a shock. For non-shockable rhythms, high quality CPR with minimal interruptions remains a key priority alongside drug therapy and seeking to identify and treat reversible causes.

Airway Management

Large randomized controlled trials (RCTs) in OHCA have failed to show a benefit between the options of bag-mask ventilation, supraglottic airway use, and tracheal intubation [17]. Evidence on the optimal airway device during in-hospital resuscitation is limited, but should be addressed by the upcoming AIRWAYS-3 trial. Based on the current evidence, ILCOR suggests that the decision on which type of airway should be used in cardiac arrest is tailored to reflect the skills of those providing airway management [18]. In systems with low to medium intubation success rates, priority should be given to using supraglottic airways.

Where those providing airway management are highly skilled and regularly undertaking tracheal intubation with a high success rate (> 95%), tracheal intubation may be considered [5].

Drugs

The PARAMEDIC2 trial, which enrolled 8014 patients with OHCA, showed that epinephrine (1 mg given every 3–5 min) was highly effective at restarting the heart [19]. The effects on long-term survival were less pronounced with a number needed to treat of 112 to improve survival at 30 days. The study did not find evidence of improved survival with a favorable neurological outcome but there was a higher rate of organ donation in those treated with epinephrine [20]. An economic evaluation

reported that when the societal benefits of organ donation were included in economic modeling, treatment with epinephrine had a 90% chance of being cost effective with a threshold of 34,500 Euro. A post hoc analysis highlighted that the earlier ALS was initiated, the greater were the chances of survival with a favorable neurological outcome [21]. ILCOR recommends the administration of epinephrine during CPR for both shockable and non-shockable rhythms [18]. The ALS Task Force highlights that neurological injury occurs following several minutes of cardiac arrest and that it is not possible at the time of starting resuscitation to identify those most at risk of neurological injury. Therefore, administering a drug that improves ROSC and survival gives an opportunity to provide high quality post-resuscitation care with the aim of reducing adverse neurological outcomes.

Meta-analyses of high dose epinephrine, vasopressin and the combination of epinephrine and vasopressin compared with standard dose (1 mg) epinephrine found low certainty evidence of improved ROSC for high dose epinephrine only. There was no improvement in long-term survival or favorable neurological outcome for any of these interventions [22]. ILCOR therefore suggests not using vasopressin routinely with or without epinephrine [18]. A trial which assessed the combination of vasopressin and steroids in addition to standard care amongst 512 patients with IHCA was published after the most recent ILCOR treatment recommendations [23].

The trial showed a 9.6% (95% confidence interval [CI] 1.1–18.0%) increase in ROSC but no difference in survival to 30 days or survival with a favorable neurological outcome. While the evidence will be assessed by ILCOR, it seems unlikely, given the absence of benefit on long-term outcomes, that treatment guidelines will change as a consequence.

A systematic review identified 14 randomized trials and 17 observational studies assessing the use of anti-arrhythmic drugs in patients with in- or out-of-hospital cardiac arrest and shock-refractory pulseless ventricular tachycardia/fibrillation (VT/VF) [24]. ILCOR's assessment of the evidence led to a weak recommendation in support of amiodarone or lidocaine based on the pre-defined subgroup analysis of bystander witnessed cardiac arrest observed in the ROC-ALPS study [25, 26]. The certainty of evidence was too low for ILCOR to make a recommendation about the use of bretylium, nifekalant, or sotolol for the treatment of adults in shock-refractory cardiac arrest.

Route of Drug Administration

Given the time critical nature of cardiac arrest, the route of drug administration is an important consideration. Early guidelines described the use of intracardiac

epinephrine, but this practice was subsequently abandoned because of the risk of misplacement and complications. Enthusiasm for endobronchial delivery via a tracheal tube also reduced based on experimental studies showing sub-optimal absorption [27]. Drug delivery through a correctly positioned central venous cannula will deliver drugs to the central circulation more rapidly than a peripheral venous cannula. However, the time taken to cite a central venous catheter *de novo* during CPR and the risk of complications likely outweigh the benefits [28].

The peripheral venous route is used most frequently during cardiac arrest treatment, supplemented with a fluid bolus to reduce drug transit time to the central circulation. The intraosseous route provides access to the rich intra-medullary venous network. Experimental studies have shown similar transit times and drug concentrations compared with the intravenous route [27]. Both observational studies and RCTs suggest that the intraosseous access is quicker and has a higher first attempt success rate than venous access. Meta-analyses of observational studies are often limited by resuscitation time bias as it is difficult to separate the effects of time of drug administration from route (intravenous versus intraosseus) [29]. ILCOR has called for further research on the optimal route of drug administration, something which is hoped will be answered through the PARAMEDIC3 trial (ISRCTN: 14223494).

Extracorporeal Cardiopulmonary Resuscitation

Extracorporeal cardiopulmonary resuscitation (eCPR) has been used during IHCA and OHCA when traditional attempts to achieve ROSC have failed. A recent systematic review identified 25 observational studies [30]. Although eCPR was feasible, there was wide heterogeneity in study design and outcomes and inconsistency between results. Studies were assessed as being at critical risk of bias leading to overall very low certainty evidence. Authors of two small RCTs have published their experience of eCPR. In a single-center RCT in Minnesota (USA), 30 patients with OHCA were randomized to eCPR or standard ALS after arrival in the emergency department. Six of 14 (43%) patients in the eCPR arm survived to hospital 162 discharge compared with 1 of 15 (7%) in the standard care arm (risk difference 36.2%, 3.7–59.2; posterior probability of eCPR superiority 0.9861) [31]. A small feasibility trial randomized in a 4:1 ratio adults with OHCA to expedited transport for eCPR or standard care. Among 151 patients assessed, 15 were enrolled of which only 5 were eligible for and treated with eCPR [32]. None of the patients enrolled in the study survived with a good neurological outcome. Both studies were characterized by low enrolment rates compared with the overall population of OHCA, matching clinical experience that only few patients with cardiac arrest may be eligible for eCPR. This raises uncertainty about the equality of access to this treatment. ILCOR's most recent treatment recommendation is to consider eCPR as a rescue therapy for selected patients with cardiac arrest when conventional CPR is failing in settings in which it can be implemented (weak recommendation, very lowcertainty evidence) [33].

Post-resuscitation Care

Most patients who achieve ROSC will be comatose in the hours to days that follow [34]. Although there are factors in the initial history and response to treatment that are associated with adverse outcome (e.g., prolonged cardiac arrest duration, unwitnessed event, absence of bystander CPR, initial non-shockable rhythm), none are able to predict outcome with sufficient precision to guide treatment escalation decisions by themselves [35]. Clinicians are advised to consider the specific circumstances of an individual's cardiac arrest, their response to treatment, associated comorbidities and frailty, alongside the patient's values and preferences (where known) in relation to the range of outcomes that can occur after cardiac arrest (death, severe neurological impairment through to good quality survival). An individualized treatment plan can then be developed for the patient [35].

Guidelines for the initial phase of care following ROSC take the clinician through a systematic assessment of the patient which seeks to normalize physiology and identify and treat the underlying cause of cardiac arrest (Fig. 2).

Coronary Angiography and Percutaneous Coronary Intervention

A 12-lead EKG may help identify evidence of an acute coronary syndrome as a potential cause of the cardiac arrest. Those who have ST elevation on their EKG should be considered for urgent coronary angiography and, if indicated, percutaneous coronary intervention (PCI) if this can be achieved within 120 min of diagnosis [4]. Where this is not possible, consideration should be given to providing pre-coronary angiography fibrinolytic therapy. For those without ST elevation, further diagnostic work up (including echocardiography and exploration of non- cardiac causes of cardiac arrest) may help with the decision relating to the need for and timing of coronary angiography [4, 36]. Those with a suspected cardiac cause and evidence of on-going ischemia and/or hemodynamic compromise may benefit from early coronary angiography $\pm$ PCI and should be discussed within the multidisciplinary team [4, 33].
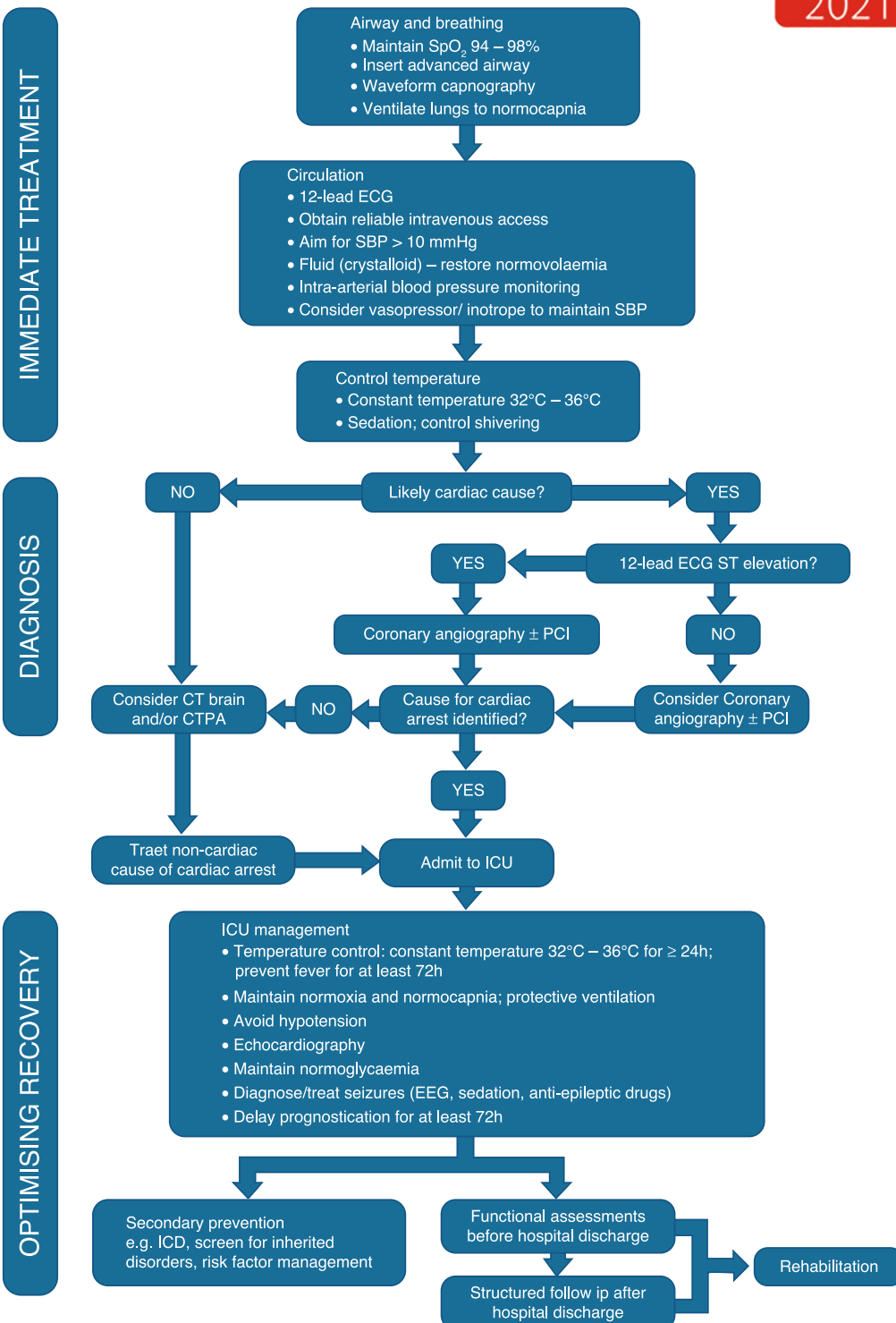
Fig. 2 Post resuscitation care algorithm (reproduced with permission from the European Resuscitation Council [6]). *SBP* systolic blood pressure, *PCI* percutaneous coronary intervention, *CTPA* computed tomography pulmonary angiogram, *ICU* intensive care unit, *EEG* electroenceph-alography, *ICD* implanted cardioverter defibrillator

Temperature Management After Cardiac Arrest

Temperature management after cardiac arrest has been one of the most studied postresuscitation care interventions. Early observational and randomized controlled trials suggested that treating those who were comatose after cardiac arrest with controlled hypothermia (circa 32–34 °C) improved survival and neurological outcomes, leading to recommendations for its inclusion in postresuscitation care treatment guidelines. The Targeted Temperature Management (TTM) 1 study compared mild (36 °C) hypothermia with moderate hypothermia (33 °C) and found no difference in the rate of survival or favorable neurological outcomes between groups, leading to guidelines being updated to recommend a constant temperature in the range of 32–36 °C. Observational studies tracking the outcomes of patients following change to practice guidelines in light of these recommendations have suggested an increase in mortality, although there is some uncertainty in these findings because of likely confounding caused by the effect of temperature on the physiological values used for statistical adjustment [37, 38]. The most recent, large multicentre TTM2 trial compared moderate hypothermia (33 °C) with avoidance of pyrexia ($\leq$ 37.5 °C) over 28 h [39]. The study found no difference in death or unfavourable neurological outcome at 6 months: 488/881 (55%) in the hypothermia group versus 479/866 (55%) in the normothermia group (relative risk 1.00 [95% CI 0.92–1.09]).

The rate of cardiac arrhythmia was higher in the intervention group (25% versus 17%). The TTM2 study prompted ILCOR and others to update a systematic review [40] and undertake a network meta-analysis [41]. The conclusion from these reviews was that the evidence does not support the routine use of induced hypothermia following cardiac arrest. ILCOR recommendations are in the process of being updated (see costr.ilcor.org) to focus on fever prevention rather than routinely inducing hypothermia to a specific target. Future research may help to identify whether specific sub-groups of patients may benefit from active cooling, as well as the optimal timing and methods for initiating cooling.

Neuroprognostication

Prognostication is an important part of the care pathway for the post-cardiac arrest comatose patient. For people who are predicted to make a good recovery, it can provide hope for the person's family and justification for the continuation of life support. For those predicted to have a poor outcome (death or survival with severe disability or unresponsive wakefulness syndrome), it enables an informed d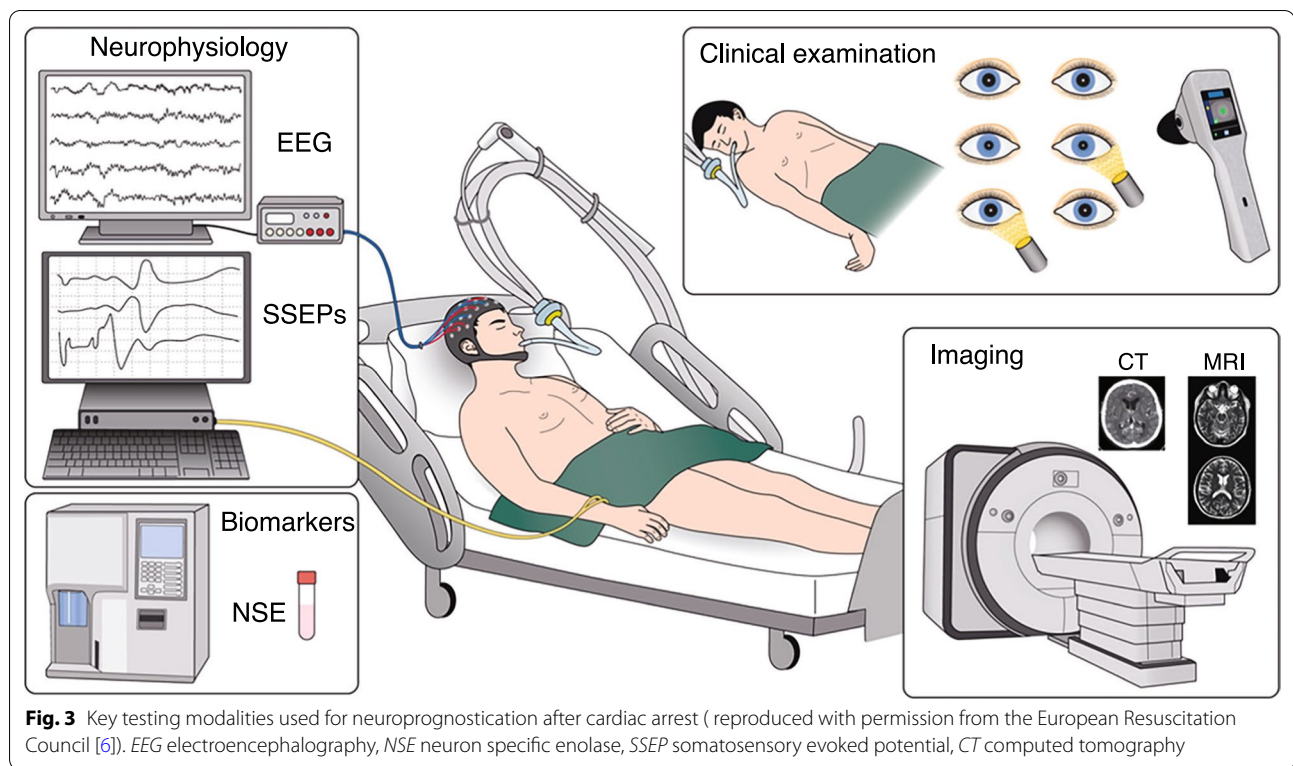iscussion with families about treatment options which might include withdrawal of life sustaining treatment. Given the high stakes of the outcome following prognostication it is important that assessments for an adverse outcome have a very low false positive rate—otherwise there is a risk of premature withdrawal of life sustaining treatment in patients who might otherwise survive.

Most initially comatose patients who will go on to make a good neurological recovery wake up within the first few days of intensive care admission [42, 43]. The ERC and the European Society of Intensive Care Medicine (ESICM) prognostic algorithm recommends that clinicians consider prognostication at least 72 h after intensive care unit (ICU) admission in patients who have a motor response of $\leq$3 on the Glasgow Coma Scale [6, 44]. Care is advised to avoid major confounders which include analgesia and sedation, neuromuscular blocking drugs, hypothermia, severe hemodynamic instability, or significant metabolic disturbance (e.g., glucose, blood gases, electrolytes). No single predictor is 100% accurate, therefore a multimodal strategy is required to minimize the risk of false positive tests leading to premature withdrawal of life sustaining treatment. Figure 3 illustrates the main testing modalities used in neuroprognostication.

Factors associated with a lower false positive rate for an adverse neurological outcome include [6, 43, 44]:

- No pupillary and corneal reflexes at $\geq$ 72 h.
- Bilateral absence of N20 somatosensory evoked potential wave.
- Highly malignant electroencephalogram (EEG).
- Neuron specific enolase > 60 μg/l at 48 and or 72 h.
- Status myoclonus within the first 72 h.
- Diffuse and extensive anoxic injury on brain computed tomography (CT) or magnetic resonance imaging (MRI).

The presence of at least two of these adverse signs suggests a high probability of a poor neurological outcome. Where none or only one of these tests is positive, then the patient should be observed and reassessed. Among this intermediate category, approximately 14% will achieve a good recovery [45]. Although the current prognostication guidelines focus on the prediction of a poor neurological outcome, there are also predictors of a good neurological outcome (e.g., a benign EEG recorded within 24 h of ROSC [46]) and guidelines on the use of these are being formulated. Where predictors of a good outcome coexist with those of a poor outcome (i.e., conflicting predictors) it may be appropriate to wait and reassess.

Fig. 3 Key testing modalities used for neuroprognostication after cardiac arrest (reproduced with permission from the European Resuscitation Council [6]). *EEG* electroencephalography, *NSE* neuron specific enolase, *SSEP* somatosensory evoked potential, *CT* computed tomography

Conclusion

Cardiac arrest remains an important cause of morbidity and mortality. Evidence based resuscitation treatment guidelines enable clinicians to incorporate best evidence into practice. High quality CPR, rapid defibrillation, and early treatment with epinephrine improve survival. Anti-arrhythmic drugs may be considered in those with shock-refractory cardiac arrest. Post-resuscitation care should focus on identifying and treating reversible causes of cardiac arrest and restoring normal physiology. The evidence highlights that clinicians should prioritize avoidance of pyrexia over any specific hypothermia temperature targets. Careful attention to the timing of prognostication (no earlier than 72 h) and use of multimodal tests to assess prognosis will help inform difficult decisions regarding the continuation or withdrawal of life-sustaining treatments.

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GDP and JPN conceived, drafted and approved the final version to be published.

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Not applicable.

Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
Not applicable.

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